UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,341	06/25/2002	David Michael Shaw	117-385	9257

23117 7590 07/01/2004

NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,341	SHAW ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/13/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *31802*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicants' preliminary amendments filed 03/18/02 and 10/30/03. With this, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election filed 04/13/04 in response to the written lack of unity mailed 01/14/04. Applicants have elected, with traverse, invention I, claims 1-25, and the species, influenza virus; *E. coli*; *E. coli* fimbrial antigen; and human allergen. Applicants' traversal is on three grounds: a) no undue burden; b) international examination of claims 1-30 ; and c) unity of invention. Applicants state that they disagree with the Office's contention that claims 1-30 lack unity of invention. Applicants submit that the Office's conclusion that Grangette *et al.* (*Immunol. Lett.* 69: 176, 1999) teach the invention is premature because no such rejection of the claims was made, and Applicants had no opportunity to respond. Applicants assert that claims 1-30 be examined together because they are so linked as to form a single general inventive concept under PCT Rule 13.1. With regard to the antigens of disparate structure and immunogenic specificity listed in claim 7, Applicants contend that the invention is directed to a bacterium. With respect to the election of species, Applicants state that the traversal of species election is not based on the species being clearly unpatentable or obvious over each other. Applicants assume that the election of species in claims 5-8 is related to a lack of a single general inventive concept. Applicants request the Office to cite the legal authority for requiring an election of species under the lack of unity practice which applied to PCT national-stage applications. Applicants request that upon indication of allowability of the claimed vaccine or bacterium, the process claims be rejoined pursuant to *In re Ochiae*, 37 USPQ2d 1127 (1995) and *In re Brouwer*, 37 USPQ2d 1663 (1996).

Applicants' arguments have been carefully considered, but are non-persuasive. At paragraph 3 of the Office Action mailed 01/14/04, the Office did cite the PCT Rule(s) that require an election of species under the lack of unity practice as applied to PCT national-stage applications. In order to show that the special technical feature does not define over the prior art, there is no requirement that an art rejection of the claims should be made concurrently in a written lack of unity. Whether or not all claims were searched or examined together during the international phase of examination in a

different country is irrelevant. That the search performed during the international phase was deficient and that the inventive groups identified in the written lack of unity are not so linked as to form a single general inventive concept under PCT 13.1 is evident from the prior art rejections made below. In addition to the reference of Grangette *et al.*, the reference of Pouwels *et al.* (*J. Biotechnol.* 44: 183-192, 1996), undisclosed on PTO-1449 to the Office under Rule 1.56, taught the product claimed in the instant claims, including that claimed in claim 1. See the art rejections made below. Thus, clearly, the special technical feature of invention I does not define over the prior art. The same is true with regard to the various heterologous antigen species of the instant application, because *L. plantarum* expressing a recited heterologous antigen that induces immunogenicity or protective response was already known in the art. See art rejection(s) below. Additionally, as set forth previously, the recited heterologous antigens expressed on *L. plantarum* do not share a significant antigenic make-up and thus require separate and non-coextensive searches under different classes/subclasses, for different bacterial antigens or microorganisms; different viral antigens or microorganisms; different parasitic antigens or microorganisms; and human allergen. For instance, while poliomyelitis and rotaviruses require searches under subclasses 217.1 and 215.1, *Vibrio cholerae* and *Staphylococcus aureus* require separate and non-coextensive searches under subclasses 243.1 and 261.1 of class 424. The various pathogenic organisms or heterologous antigens clearly require burdensome searches. Therefore, the lack of unity set forth in the instant application is proper and is maintained.

Since Applicants have elected the product claims, the method of using the product claims would be kept pending pursuant to the rejoinder provisions of M.P.E.P 821.04 and would be rejoined with the elected product claims if and when the latter were deemed allowable. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See 'Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C § 103(b),' 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicants are advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right rejoinder.

Status of Claims

3) Claims 1-30 are pending.

Claims 3-18, 23, 25, 28 and 30 have been amended via the preliminary amendment filed 03/18/02.

Claims 5-7, 11-15, 21 and 27 have been amended via the preliminary amendment filed 10/30/03.

Claims 26-30 are withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1-25 are under examination. A First Action on the Merits on these claims is issued.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' Information Disclosure Statement filed 03/18/02. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

5) The instant application is a national stage 371 application of PCT/GB00/03575, filed 09/18/2000 and claims foreign priority to the application, 99203056.9, filed 09/17/1999, filed in Europe. A certified copy of the foreign priority document has been submitted.

Specification - Informalities

6) The specification is objected to for the following reasons:

(a) The instant specification lacks the section, 'Brief Description of the Drawings', for Figures 1A-1D. See 37 C.F.R 1.74.

(b) The use of the trademarks in the instant specification has been noted in this application. For example: "Tween-20" at line 10 of page 31; and 'Nunc' and 'Sigma' in the last paragraph on page 30. Although the use of trademarks is permissible in patent applications, the propriety nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

7) Claims 16, 18, 19, 23 and 25 are rejected under 35 U.S.C. § 112, first paragraph, as failing to

provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological material is (1) known and readily available to the public; (2) reproducible from the written description, e.g. sequenced; or (3) deposited.

Claims 16 and 18 are directed to a specific recombinant *Lactobacillus plantarum* 256. It is apparent that the recited recombinant *Lactobacillus plantarum* 256 is required to practice the claimed invention. As a required element, the specifically recited recombinant *Lactobacillus plantarum* 256 must be known and readily available to the public, or obtainable by a reproducible method set forth in the specification. If not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the recited mutant strain at an acceptable depository. From the specification, it does not appear that the recombinant *Lactobacillus plantarum* 256 was deposited in a recognized depository. Therefore, the recombinant *Lactobacillus plantarum* 256, does not appear to be readily available to the public, and it is not certain if this specific recombinant *Lactobacillus plantarum* 256 can be reproducibly produced without undue experimentation. Since obtaining such a functional recombinant *Lactobacillus plantarum* 256 that is capable of eliciting an immune response and/or immunogenicity against the heterologous antigen is uncertain or non-predictable, undue experimentation would be required to practice the invention. Without a publicly available deposit of the recombinant *Lactobacillus plantarum* 256, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. A deposition of the recombinant *Lactobacillus plantarum* 256, would satisfy the requirement of 35 U.S.C. § 112, first paragraph.

On the other hand, if a deposit has already been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicants or assignees, or a statement by an attorney of record who has a registration number and has authority and control over the conditions of deposit over his or her signature, is required. The statement should state that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that **all** restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced, if viable samples cannot be dispensed by the depository. This requirement is necessary when deposits are made under the provisions of the

Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state. The statement should identify the deposited strain(s) by its depository accession number, establish that the deposited strain(s) is the same as the one described in the specification/claim, and establish that the deposited strain(s) was in the Applicants' possession at the time of filing. As a means of satisfying the necessary criteria of the deposit rules and to show that the claimed bacterial strain is the same as the one deposited, Applicants may submit a copy of the contract or a notice of acceptance of the recombinant strain by the depository.

Applicants' attention is directed to *In re Lundack*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 C.F.R § 1.801-1.809 for further information concerning deposit practice.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

8) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

9) Claims 1-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and confusing in the recitation 'immune response and ..... immunogenicity', because it is unclear how one differs from the other.

(b) Claims 2-17 lack proper antecedent basis in the limitation: 'A vaccine according to claim .....'. For proper antecedence, it is suggested that Applicants replace the limitation with --The vaccine according to claim .....--.

(c) Claim 2 is vague and confusing in the limitation: 'vector capable of ..... exposure on the cell surface', because it is unclear what is encompassed in this limitation. It is not clear what is being exposed on the cell surface.

(d) Claims 3 and 15 is vague and indefinite in the recitation 'such as', because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

(e) Claims 5 and 6 are incorrect in the recitation of the name of the following pathogenic microorganism: '*Vibrio cholera*'. Correction is requested.

(f) Claim 5 is incorrect in the recitation of the names of the following pathogenic

microorganisms: '*Treponema pallidium' and 'Coxiella burnetti*'. Correction is requested.

(g) Claim 5 is incorrect and/or confusing in the recitation: 'pathogenic microorganism selected from the group consisting of..... *'Pneumocystis pneumonia*'. Is this the name of a pathogenic microorganism?.

(h) Claim 5 is vague and indefinite in the use of abbreviations in the claim language: 'EHEC'; 'ETEC'; 'EIEC'; 'EPEC'; 'EaggEC'; and 'DAEC'. It is suggested that the limitations be recited as full terminologies with the abbreviations maintained within parentheses.

(i) Claim 7 is vague and indefinite in the use of an abbreviation in the claim language: 'CFA'. It is suggested that the limitation be recited as a full terminology with the abbreviation maintained within parentheses.

(j) Claim 5 is vague, indefinite and confusing in the recitation: 'EPEC strains of *E. coli* EaggEC strains of *E. coli*'. Does this phrase represent a single group of pathogenic microorganism?

(k) Claim 9 is indefinite in the limitation: 'can induce protective immunogenicity', because it is unclear the protective immunogenicity is directed to or against what?

(l) Claim 11 is confusing and/or incorrect in the limitation: 'and/or an the cell surface'. The phrase makes no sense.

(m) Claim 18 is vague, indefinite and confusing in the limitation: 'as defined in vaccine claim 1'. The meaning or scope of the phrase is not understood.

(n) Claim 23 is vague, indefinite, confusing and/or lacks proper antecedent basis in the limitation: 'A *Lactobacillus* organism according to claim 18 which is *L. plantarum*'. Claim 18 is already directed to a recombinant *Lactobacillus plantarum*. Furthermore, claim 23 is improperly broadening in scope, because the term *'Lactobacillus* organism' is broader than the term 'recombinant *L. plantarum*' of claim 18.

(o) Claim 15 is confusing and/or incorrect in the recitation: 'adminsitrat ion'.

(p) Claim 15 is confusing and vague in the limitation: '*Lactobacillus plantarum* is a recombinant *Lactobacillus plantarum* 256'. Does it mean that there are more than one *Lactobacillus plantarum* 256.

(q) Claims 19, 21 and 25 lack proper antecedent basis in the limitation: 'A bacterium according to claim ...'. For proper antecedence, it is suggested that Applicants replace the recitation

with --The bacterium according to claim ...--.

(r) Claim 21 has improper antecedence in the limitations: 'bacterium according to claim 20 wherein **the** naturally occurring or unmodified *L. plantarum*' [Emphasis added], because claim 20 does not recite any 'naturally occurring or unmodified *L. plantarum*'.

(s) Claim 22 is confusing and/or incorrect in the limitation: 'elicit an immune response *to an* individual' as opposed to --in an individual --[Emphasis added].

(t) Claims 2-19, 21, 23 and 25, which depend directly or indirectly from claim 1 or 20, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

10) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11) Claims 1-7 and 9-25 are rejected 35 U.S.C. § 102(b) as being anticipated by Pouwels *et al.* (*J. Biotechnol.* 44: 183-192, 1996) (Pouwels *et al.*, 1996) as evidenced by Hoshino *et al.* (*J. Virol.* 62: 744-748, 1988, abstract) or Virelizier JL (*J. Immunol.* 115: 434-439, 1975, abstract), Naidu (US 20020192202 A1) and Wells *et al.* (*Antonie van Lewuwenhoek* 70: 317-330, 1996 - Applicants' IDS) (Wells *et al.*, 1996).

Pouwels *et al.* (1996) taught an oral vaccine comprising a recombinant *Lactobacillus plantarum* capable of expressing, intracellularly, the viral antigenic determinant, VP7 (i.e., a heterologous antigen), of porcine rotavirus (i.e., a pathogenic microorganism that colonizes the GI tract) and/or beta-galactosidase (i.e., a heterologous antigen). See page 187; and Tables 1 and 2. *Lactobacillus plantarum*, ATCC 8014, ATCC 14917, and NCIB 8826 containing a plasmid pLP503-HA expressing an epitope of the influenza virus haemagglutinin and beta-glucuronidase are taught (se section 3.4). The transformants expressing HA-beta-glucuronidase, on dilution and oral administration into mice, elicited a significant immune response to the HA-beta-glucuronidase (see last five lines in right column on page 190; and section 3.5. The fact that the transformant

Lactobacillus plantarum was diluted and administered to mice (see section 3.5) indicates that the prior art vaccine inherently comprised a pharmaceutically acceptable carrier. *Lactobacillus plantarum*, ATCC 8014, is described as an intrinsic adjuvant by itself (see page 186, left column). That the VP7 rotaviral antigen or the influenza viral haemagglutinin antigen serves as a protective immunogen is inherent from the teachings of the prior art in light of what was known in the art. For example, Hoshino *et al.* and Virelizier respectively taught protective nature of the porcine VP7 antigen and influenza haemagglutinin antigens (see abstract). That one of the prior art recombinant *L. plantarum*, ATCC 14917, is from a non-human source and that the other recombinant *L. plantarum*, NCIB886, persists in the GI tract for about 9 days, are also inherent from the teachings of the prior art as is known in the art. For instance, Naidu teaches *L. plantarum*, ATCC 14917 isolate, to be from pickled cabbage (see Table 1), and Wells *et al.* (1996) taught that recombinant *L. plantarum*, NCIB886, persists in the GI tract for about 9 days (see Table 1).

Although Pouwels *et al.* (1996) do not expressly recite the recombinant *L. plantarum*'s persistence in the vaccinated subject for longer periods compared to that of *L. plantarum* 80 or *NCIMB 8826*, such longer persistence is viewed as an inherent property of the prior art recombinant *L. plantarum*. The Office's position that Pouwels' (1996) recombinant *L. plantarum* is the same as the Applicants' recombinant *L. plantarum* is based upon the fact that every structural characteristic overlapping in Pouwels' (1996) recombinant *L. plantarum* and Applicants' recombinant *L. plantarum* are the same. There is sufficient overlap between the two recombinant *L. plantarum* to reasonably conclude that the prior art recombinant *L. plantarum* is one and the same as the Applicants' recombinant *L. plantarum*, and therefore, it is expected to have the same functional properties as that of the instantly claimed recombinant *L. plantarum*. In view of the lack of additional structure for the *Lactobacillus plantarum* 256 recited in claim 16, one of the *Lactobacillus plantarum* recombinants of Pouwels *et al.* (1996) is deemed to meet the claim limitation. The limitation '256' is viewed merely as a laboratory designation given to the prior art recombinant *Lactobacillus plantarum* and does not impart any structure that distinguishes the product of the prior art from the claimed product. Since the Office does not have the facilities for examining and comparing Applicants' recombinant *L. plantarum* with the recombinant *L. plantarum* of the prior art, the burden is on Applicants to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that

the recombinant *L. plantarum* of the prior art does not possess the same functional characteristics of the claimed recombinant *L. plantarum*). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

The teachings of Pouwels *et al.* (1996) anticipate the instant claims. Hoshino *et al.*, Virelizier JL, Naidu or Wells *et al.* (1996) is **not** used as a secondary reference in combination with Pouwels *et al.* (1996), but rather is used to show that every element of the claimed subject matter is disclosed by Pouwels *et al.*(1996) with the unrecited limitation(s) being inherent in view of what was known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 1-7 and 9-25 are anticipated by Pouwels *et al.* (1996).

12) Claims 20-22 are rejected are rejected 35 U.S.C. § 102(b) as being anticipated by Mercenier *et al.* (*Adv. Food Sci.* 18: 73-77, 1996).

Since claim 20, from which claim 21 depends, does not recite any *Lactobacillus plantarum,* the recitation 'the naturally occurring or unmodified *L. plantarum*' in part (a) of claim 21 does not make sense. The bacterium recited in claim 21(a) is interpreted in this rejection as the *Lactobacillus* bacterium as recited in claim 20.

Mercenier *et al.* taught a *Lactobacillus* bacterium of murine (i.e., non-human) origin, *Lactobacillus casei*, which has been modified by a recombinant technique to express a heterologous antigen, such as, M6:V3 or M6:gp41E, intracellularly or in a surface exposed form. The modified bacterium expressing M6:gp41E or M6:V3 antigen elicited a strong anti-M6 antibody response on oral or intragastric immunization (see 'Summary'; pages 74 and 75; and Figure 1). The recombinant *Lactobacillus casei* strain persisted in the intestine for 6-8 days (see page 76 and Table 1).

Claims 20-22 are anticipated by Mercenier *et al.*

Rejection(s) under 35 U.S.C § 103

13) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied

for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

14) Claims 1 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pouwels *et al.* (*Int. J. Food Microbiol.* 41: 155-167, May 1998 - Applicants' IDS) in view of Claassen *et al.* (*In: Recombinant and Synthetic Vaccines.* (Ed) Talwar GP *et al.* Narosa Publishing House, New Delhi, 407-412, 1994) and Wells *et al.* (*Antonie van Lewuwenhoek* 70: 317-330, 1996 - Applicants' IDS) (Wells *et al.*, 1996).

Pouwels *et al.* (1998) taught a recombinant *L. casei* intracellularly expressing TTFC and a composition comprising the same, which did elicit antibodies after oral immunization. The antibody levels were however low due to the poor viability of this strain in the mammalian gut. Pouwels *et al.* (1998) identified the persistence of lactic acid bacterial strains in the gut to be an important parameter in the selection of strains that can be used for immunization. Pouwels *et al.* (1998) taught that a variety of *Lactobacillus* strains have been identified as strains that could persist for 5-7 or 20 days. Pouwels *et al.* (1998) expressly suggest such strains which persist longer, to be more suitable for immunization than the *L. casei* strain. See pages 163-165.

Pouwels *et al.* (1998) do not teach an immunogenic oral vaccine comprising *L. plantarum* expressing a tetanus antigen intracellularly.

However, Claassen *et al.* expressly taught that it has become possible to transform virtually any *Lactobacillus* with simple plasmid vectors, including *L. plantarum*. Claassen *et al.* taught that *L. plantarum, L. casei, L. pentosus, L. acidophilus, L. fermentum* and *L. brevis* are routinely transformed with plasmids by making use of electroporation technique, and that the transformants can stably or transiently express a foreign antigen or heterologous proteins, and neutralizing or protective epitopes, including rotaviral VP7 and FMDV epitopes. These transformants are taught to serve as food-grade vectors for use in humans (see paragraph bridging pages 400 and 411).

Wells *et al.* (1996) taught a strain of *Lactobacillus plantarum*, NCIB 8826, which has the

capacity to persist in the mammalian gastrointestinal tract for as long as about 9 days. See Table 1.

Given Pouwels' (1998) express suggestion that *Lactobacillus* strains which persist longer are more suitable for immunization than the *L. casei* strain, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Pouwels' (1998) poorly viable *L. casei* with Wells' (1996) *L. plantarum* to produce the vaccine of the instant invention. One of skill in the art would have had a reasonable expectation of success in obtaining the claimed product given the express teaching by Claassen *et al.* that virtually any *Lactobacillus* including *L. plantarum* can be routinely transformed with plasmid vectors to stably or transiently express a foreign antigen or heterologous protein, or a neutralizing or protective epitope. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of providing, advantageously, an oral vaccine comprising a *Lactobacillus* strain, which unlike Pouwels' (1998) poorly viable recombinant *L. casei*, has been demonstrated in the art to persist in the mammalian GI tract for as long as 9 days as taught by Wells *et al.* (1996).

Claims 1 and 8 are *prima facie* obvious over the prior art of record.

Remarks

15) Claims 1-25 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

18) Any inquiry concerning this communication or earlier communications from the Examiner

should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER